Chapter 23
Anal Dysplasia/Cancer: Management of Patients with AIN 3

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Pt population	Intervention	Comparator	Outcome studied
Pts with AIN 3	HRA	Clinical followup	Cancer prevention, cost

Introduction

Anal squamous cell carcinoma (ASCC) is an uncommon malignancy caused by infection with oncogenic strains of *Human papilloma virus* (HPV). The precursor lesion, anal intraepithelial neoplasia III(AIN III) or high-grade squamous intraepithelial lesion (HSIL), has a similar causal association with HPV [1–3]. Although HPV infections are extremely common, peaking in the third decade of life, they are usually transient with evidence of infection absent by the end of that decade. This tends not to be true in high-risk groups – those who practice anoreceptive intercourse and those immunocompromised from drugs or disease. The frequency of progression of HSIL to anal squamous cell cancer is uncertain, but has an estimated risk in the range of 8.5–13 % [2–4].

Despite the known association of HSIL and anal squamous cell carcinoma, many patients go undiagnosed, or potentially worse yet, diagnosed and not treated. Many factors contribute to the lack of treatment. Historically, poor adoption of preventative techniques resulted from a lack of standardized definitions and treatment patterns, leaving treating physicians confused regarding evidence-based practice. In addition, a lack of clear screening guidelines for low risk patients (eg heterosexual females who do not practice receptive anal intercourse) resulted in affected patients

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being missed owing to the misconception that this was a disease limited to men who have sex with other men (MSM) and/or men and women who are HIV positive.

There has been relatively limited adoption of high-resolution anoscopy (HRA) likely owing to unfamiliarity with the equipment and poor physician reimbursement. Further, there continues to be a lively ongoing debate regarding the necessity and cost effectiveness of this treatment modality when compared to simple observation and clinical followup. The argument is that the relatively small subset of patients who do progress from HSIL to anal carcinoma can be identified early and treated successfully, without exposing the entire cohort to serial HRA. However, the 5-year survival for Stage I and Stage IV anal cell cancer remains at 80 % and 30 % respectively [5]. Thus, withholding treatment until a patient has developed anal squamous cell cancer, even in the setting of stage I disease,, may result in avoidable mortality from the disease not to mention the morbidity of chemoradiation therapy.

For the trained clinician, whether it is an advanced practice provider or physician, the screening tools (anal cytology and HRA) are relatively simple and cost effective [6]. However, no RCTs have shown that such screening programs are efficacious at reducing anal cancer incidence and mortality. Many believe that this is because the procurement techniques for anal cytology and the performance of HRA are highly variable and non-standardized. Fortunately, trials are currently underway in order to evaluate the efficacy of cancer prevention with screening and treatment. Further, national guidelines published by the National Comprehensive Cancer Network (NCCN) and American College of Colon and Rectal Surgeons (ASCRS) are now able to make recommendations based on higher quality of evidence [7, 8].

Search Strategy

An electronic search of the PubMed database was performed to obtain key literature in the field of anal cancer published between January 1 2000 and July 1 2015, using the following search terms: (anal cancer) OR (anal squamous cell carcinoma) OR (high-grade squamous intraepithelial lesion). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer reviewed biomedical literature, and is used by the NCCN when formulating updated guidelines. The search results were narrowed by selecting studies in humans published in English with full-length text. Results were then confined to the following article types: clinical trial, Phase II; Clinical trial, Phase III; Clinical Trial, Phase IV; practice guidelines, randomized controlled trial, meta analysis, systematic reviews, and validation studies. The PubMed search resulted in 17,299 citations and their potential relevance was examined. When ‘and treatment’ was added to the search terms, 15,227 items were resulted. These were sorted by relevance to improve detection of relevant studies.

The National Comprehensive Cancer Network (NCCN) and American College of Colon and Rectal Surgeons (ASCRS) were then searched for additional relevant studies for inclusion. This did not result in any further inclusion that was not found in the PubMed search.

Results

Prevention

Prior to discussing treatment of AIN, brief mention will be made of prevention. A quadrivalent HPV vaccine is currently available, and has been proven effective in preventing high-grade cervical intraepithelial neoplasia related to HPV strains 6, 11, 16 or 18 in women, and genital lesions associated with the same HPV strains in men [9–11]. Thus, a study was prompted to look at the efficacy of the vaccine for prevention of HSIL and ASCC in MSM [12]. Although none of the 602 healthy men aged 16 to 26 developed ASCC within the 3-year follow-up period, there were 5 cases of grade HSIL in the vaccine arm and 24 cases in the placebo arm. This amounted to an observed efficacy of 77.5 % for prevention of HSIL, suggesting the quadrivalent HPV vaccine may reduce the risk of ASCC in this patient population.

Recently, the quadrivalent HPV vaccine has been tested in HIV positive children, a group at high risk for HPV, and subsequent associated cervical and anal cancer. A randomized clinical trial found the vaccine to be safe and immunogenic in 126 HIV positive aged 7–12 years. Initially, antibody titers were lower for HPV 6 and 18 compared with historic age-matched immunocompetent controls [13], but this difference was lost after the fourth dose of vaccine [14]. The success of vaccines could lead to a significant decrease or near elimination of ASCC if used early and universally. Thus, their clinical importance cannot be underscored enough.

Patients with condyloma acuminatum or low-grade squamous intraepithelial lesion (LSIL) have very low potential for malignancy [15]. It is not clear that LSIL actually directly progresses to HSIL or ASCC. Rather, LSIL may be a marker in certain at risk groups for the presence of virus. Those patients that are symptomatic may wish to have the lesions excised or destroyed and this can be done with cautery, IRC or chemical agents. Follow up of these patients depends heavily on age, risk factors, underlying disease states and behavior patterns.

Treatment

The goal of treating HSIL is the prevention of ASCC while maintaining anal function, including continence of stool and gas. Several therapies are available for the treatment of HSIL including surgical excision, electrocautery, topical imiquimod, trichloracetic acid and topical fluorouracil (5-FU). Limited studies, largely in the form of case series, have addressed the relative efficacy of the potential treatment options.

In 2000, a survey of 663 members of the ASCRS found that 87 % of respondents chose surgical excision with clear margins as the optimal treatment for HSIL [16]. However, a number of subsequent studies have suggested that surgery may not be the best treatment approach. Brown reported 34 patients with HSIL treated

surgically in the UK. Within 41 months, 14 of 34 patients had macroscopic recurrences and 25% of patients had anal function deficits postoperatively [17]. Scholefield reported on 35 patients who underwent limited excision for HSIL and were followed for 63 months. Three of 35 (9%) had progression to ASCC [2]. Watson reported their experience with 72 patients treated surgically, of whom nine developed incontinence; four of these required a colostomy. Despite their aggressive surgical approach, 8 patients (11%) progressed to invasive ASCC [3]. These studies have suggested surgical excision is not an ideal treatment due to incomplete excisions, frequent recurrences, and complications including stenosis and incontinence. They argued further that because chemoradiation for small invasive anal carcinoma is effective, a less radical approach may be warranted, because early surgical intervention with the associated complications may compromise later definitive treatment.

Other investigators suggest that rather than using an excisional approach, the use of HRA allows targeted destruction of suspicious lesions with the lowest reported rates of progression to cancer and preservation of anorectal function. HRA is used to identify dysplastic epithelium under the magnification of a standard colposcope or operating microscope. The technical application of HRA itself is discussed in more detail in the section regarding our treatment approach; but, briefly, HRA can be used with either targeted infrared coagulation (IRC) or electrocautery (EC). Both procedures are outpatient with only enemas given in preparation. IRC can be used with facility for lesions above the dentate line although local anesthesia is often necessary because the heat generated by the instrument causes pain. It coagulates lesions using 1.6 s pulses until the entire surface and an approximately 3 mm surrounding border are coagulated. The coagulated tissue is then scraped off with a small cotton Q-tip or forceps. This is repeated until the submucosal vessels are identified and coagulated. HRA directed EC, unlike IRC, uses bipolar cautery creating a smoke plume that requires a smoke evacuator to prevent transmission of HPV. Across the four listed studies (Table 23.1) regarding HRA targeted IRC for HSIL, there was no reported anal function compromise, 10–38% had recurrence of HSIL, and none had progression to ASCC [18–21]. Similarly, in the two listed studies regarding HRA targeted EC, there was no reported anal function compromise, 17–31% had recurrence of HSIL, and 0.4% had progression to anal squamous cell carcinoma [22, 23]. Of note, recurrence of HSIL was higher in HIV patients and patients with higher burden of disease.

The use of topical medical treatments has recently become more widespread. Topical fluorouracil (5-FU) and imiquimod have the advantages of treating AIN by the patient themselves without compromising anorectal function. However, topical treatments have the disadvantage of extended treatment courses and significant side effects including perianal pain and irritation that may result in non-compliance. Treatment with 5-FU is not standardized. The amount and frequency are variable. Despite several treatment interruptions due to side effects and variable protocols administered, there has been very little progression to ASCC. Only one patient among the three studies listed in Table 23.1 had progression to ASCC [24].

Table 23.1 Treatment practices for HSIL

Study ID	Patients	Anal function compromised (%)	HSIL at last f/u (%)	Developed ASCC (%)	Grade of evidence (GRADE system)
Surgery					
Excision					
Watson et al. [3]	10/62 immunocompromised	13	Not reported	11	Moderate
Scholefield et al. [2]	6/35 immunocompromised	0	Not reported	9	Moderate
Devaraj and Cosman [4]	40 HIV + MSM	3	Not reported	8	Moderate
Brown et al. [17]	34 M and F	15	Not reported	0	Moderate
Marchesa et al. [36]	16 M, 31 F	0	38 %	6	Moderate
HRA-targeted IRC					
Goldstone et al. [19]	52 HIV-MSM/44 HIV + MSM	0	HIV + 18 %; HIV-10 %	0	High
Weis et al. [21]	99 M/25 F all HIV+	0	Treated 13 %; untreated 93 %	0	Moderate
Stier et al. [37]	16 M/2 F all HIV+	0	38 %	0	Moderate
Cranston et al. [18]	68 HIV + MSM	0	36 %	0	Moderate
HRA-targeted EC					
Marks and Goldstone [22]	132 HIV + MSM; 100 HIV-MSM	0	HIV + 31 % HIV-17 %	0.4	High
HRA-targeted EC f/u IRC or TCA					
Pineda et al. [33]	194/246 immunocompromised	0.8	22 %	1.2	High
Topical medical therapy					
5-FU					
Snyder et al. [29]	11 HIV + MSM	0	72 %	0	Moderate
Richel et al. [28]	46 HIV + MSM	0	30 %	0	Moderate
Graham et al. [24]	1/9 HIV+	0	13 %	13 (n = 1)	Low

(continued)

Table 23.1 (continued)

Study ID	Patients	Anal function compromised (%)	HSIL at last f/u (%)	Developed ASCC (%)	Grade of evidence (GRADE system)
Imiquimod					
Wieland et al. [30]	28 HIV + MSM	0	9 %	0	Moderate
Kreuter et al. [27]	10 HIV + MSM	0	Not reported	0	Low
Fox et al. [25]	64 HIV + MSM	0	39 %	3	High
Van der Snoek et al. [38]	44 HIV + MSM	Not reported	34 %	Not reported	Low
TCA					
Singh et al. [39]	54 MSM; 35 HIV+	0	39 %	0	Moderate
Cranston et al. [18]	72 HIV+ MSM	Not reported	20 %	Not reported	Moderate
RCT					
Richel O et al. [26]	246 HIV + MSM	0	At 72 weeks: 71 % imiquimod; 58 % 5-FU; 68 % EC	1.2 % (n = 3)	High

Similarly the use of topical imiquimod 5 % cream applied three times weekly has been associated with very little progression to ASCC, with only one series reporting 2 patients with progression (3 %) [25]. Importantly, with topical medical treatments, significant education of patients is required. Namely, patients should be told that symptoms of itching, burning, and pain are evidence that imiquimod is working and is not a sign that treatment should be discontinued. Additionally, imiquimod can actually cause transient flu like symptoms the day following treatment. If patients do not develop signs of erythema or erosions, the imiquimod frequency can be increased throughout the treatment course. Unfortunately, the adherence rate of topical imiquimod is low due to these side effects, and therefore make this treatment strategy less effective.

Recently, RCTs are beginning to compare the aforementioned treatment approaches. A recent RCT looking at 246 HIV-positive MSM found that electrocautery had significantly increased rates of complete resolution compared to both topical imiquimod and topical fluorouracil, and concluded that EC was the superior treatment option [26]. Recurrence rates of HSIL were high in all treatment groups underscoring the need for frequent surveillance and follow up. At week 24, 48 and 72, 22 %, 46 %, and 67 % of patients had recurrence respectively. Specifically, recurrence at 72 weeks was found in 71 % (n = 10/14) of patients treated with imiquimod,

58 % (n = 7/12) of patients treated with 5-FU, and 68 % (n = 13/19) of patients treated with EC. Treatment side-effects, most commonly pain, bleeding and itching were significantly more common in the imiquimod and 5-FU group at 43 % and 27 % respectively, as compared to 18 % in the electrocautery group.

Expectant Management

It has been suggested by many that expectant management may be an appropriate, cost effective approach for HSIL rather than treatment, as there are no associated treatment costs or side effects. A trial addressing this approach was conducted at a university and VA practice. Forty 40 HIV infected patients were followed for a mean of 32 months [4]. Patients had a clinical exam every 6 months, and biopsies of new macroscopic or symptomatic disease. Of the 40 patients, 23 had HSIL. Three of the 28 patients developed ASCC at 10, 16 and 84 months, all of whom had a cancer less than 2.5 cm in diameter. This trial suggested that very few patients progress to cancer, and, if so, were diagnosed at an early stage. To better understand this question, a large ongoing randomized phase III trial comparing topical or ablative treatment with active monitoring in HIV-positive patients with HSIL is currently ongoing. The primary measure is time to anal cancer. The study is estimated to be completed in 2022 (clinicaltrials.gov NCT02135419) and may provide additional answers regarding active monitoring versus treatment in a high-risk group with HSIL. No trials are currently underway for low risk patient cohort with HSIL, likely because there are so few patients, and even fewer who progress to ASCC.

Recommendations Based on the Data

Several limitations exist when interpreting the aforementioned data. Studies of HSIL screening and treatment practices are largely comprised of only immunosuppressed patients. And the single RCT to date includes only high risk HIV+ MSM, limiting the applicability of the results to other patient cohorts. Treatments reported for HSIL are not standardized, and reports of treatment outcome are mainly in the form of case series and open-label studies, with only the one aforementioned RCT.

Despite these limitations, there is strong evidence that HSIL, left untreated, can and does progress to ASCC [1]. Once diagnosed, these patients then require chemotherapy with radiation, and possible surgical intervention, all with associated morbidity. Several studies, albeit small in patient number, have demonstrated nearly zero progression to malignancy with both electrocautery and topical medical therapy [22, 27–30]. A RCT has suggested electrocautery is the superior ablative modality [26]. This suggests patients with HSIL should be actively treated with EC in order to prevent progression to ASCC.

Given that women have largely been left out of the discussion but develop anal cancer at a higher rate than men, consensus guidelines developed by an international panel of experts are available to guide the approach to a given patient based on their specific risk factors [31].

Personal View of the Data

There is no controversy that colonic polyps should be removed to prevent progression to colon and rectal cancer. However, there seems to be controversy regarding the definition, prognosis, method of diagnosis, surveillance, and treatment for AIN/HSIL. Part of the challenge lies in the fact that the disease prevalence is low, making RCTs difficult to perform based on a primary outcome measure of progression to cancer. Additionally, potential prevention practices with HRA have low reimbursement rates and serve as a barrier to implementation..

However, therapy with HRA targeted EC may be performed as an office based procedure without the need for anorectal preparation or narcotics upon dismissal if the lesions are above the dentate line or limited in extent. Alternatively, for extensive disease below the dentate line involving anal mucosa and or perianal skin, the patients may be treated on an outpatient basis and discharged with instructions for sitz baths, topical analgesics (5 % Lidocaine Cream – Recticare (Ferndale labs) preferred), and either Ultram, Tylenol with codeine, NSAIDS or Tylenol. HRA targeted destruction is technically straightforward and can be performed by colorectal surgeons, family practitioners, gynecologists and advanced practice providers, to name a few. The obstacles to performing HRA targeted destruction of lesions may be cost, reimbursement, clinical practice and the training required to visualize lesions via either a microscope, the colposcope or even surgical loupes. Training is readily available through the ASCCP (www.asccp.org) and may be efficiently built into one's office based practice.

As is well recognized by our readers, many patients referred for colorectal evaluation with a diverse array of symptoms and findings often come with a chief complaint of "hemorrhoids." We perform a history to document risk factors for anal dysplasia including HPV infection (anal-genital warts), history of receptive anal intercourse or sexually transmitted disease, a history of cervical vulvar or vaginal cancer, immunosuppression after solid organ transplant or HIV infection, hematologic malignancies, certain autoimmune disorders including Crohn's disease [32] and smoking. Physical exam includes perianal inspection, digital rectal exam, and anoscopy as indicated.

We prefer the operating room for the initial examination and treatment of patients with HSIL, and for needed re-treatment of extensive disease or disease complicated by synchronous anal pathology (eg overlying hermorrhoidal tissue or complicating fistulous disease). HRA in the operating room is preferred for our initial evaluation and treatment because we feel we get the best exposure with the sphincters completely relaxed with an anal block which allows for flattening of the hemorrhoidal

complexes and clear visualization of the tissues that might otherwise hide at the base of a large complex when visualized with a plastic anoscope in the office.

In the operating room, the patient is positioned prone jack knife with the buttocks taped apart. Anesthesia with MAC local with 0.25 % Marcaine in the subcutaneous tissues and 0.5 % Marcaine with 1:200,000 epinephrine in the sphincters for the anal block are administered. A thorough examination looking for hyperpigmentation, erythema, elevation, or scaling is performed. The distal rectal mucosa, anal mucosa, and perianal skin is then treated with 3 % acetic acid by placing one acetic acid soaked Ray-Tec in the anal canal and distal rectum, and one over the anus/perianal skin. We use an operating microscope for magnification. We look for a distinct vascular pattern within the acetowhitened rectal and anal mucosa or perianal skin that is characteristic of HSIL. Any concerning lesions are biopsied and then treated with needle tip cautery [23]. A deep burn is avoided by quickly moving superficially across the surface of the tissue, sparing the surrounding normal mucosa. Our experience is that we can limit the depth of injury to less than that observed with excision, which may contribute significantly to our low observed rate of complications [33]. This is safe and effective in both HIV (+) and HIV (−) men and women [34].

We inform patients with condyloma acuminatum (low-grade intraepithelial neoplasia LSIL, AIN-1) that they have a very low potential for malignancy [15]. We therefore offer treatment to symptomatic patients or those who simply want to have the lesions removed (the vast majority). In high risk groups, LSIL can be a marker for the presence of HSIL, especially in immunosuppressed populations; annual surveillance including digital anal rectal examination, anal cytology, and HRA for early detection of HSIL may be beneficial. Recently some have suggested that the rate of anal cancer is extremely low before age 30 so that close surveillance might begin after age 30 even in the high risk patients. How to follow "low-risk" patients with LSIL remains unclear. This is where routine typing of HPV may be beneficial in stratifying follow up. For patients who have been treated for HSIL, we perform a 1 and 6 month follow up examination with anoscopy.

If the patient is not involved in high risk behavior, we recommend annual surveillance, again with digital anal examination and anal cytology. If involved in high risk behavior, HRA is added to this algorithm on an annual basis. If immunosuppressed, or if the patient has "high risk disease", this interval may be shortened to 3–6 months on a case by case basis. If a recurrence is found, we treat them in the office with trichloracetic acid, IRC or hyfrecation unless the disease is complex as noted above. We, and others, have experienced excellent control of HSIL and minimal progression to cancer using this approach [19, 23, 33, 35]. We cannot comment on topical treatments as we have no personal experience with their use. However, we are referred patients who have been on them with recurrence. There may be benefit in combination with electrocautery to prevent recurrence, but this has yet to be studied.

Ultimately, the goals of treating patients with HSIL is preventing morbidity associated with the treatment of anal cancer without causing disturbances of anal function. We have low cost, outpatient tools to do this and evidence from RCT supporting

its use. We do not feel annual surveillance, in isolation, provides adequate care of our patients.

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